

Treatment of vulvovaginal candidiasis

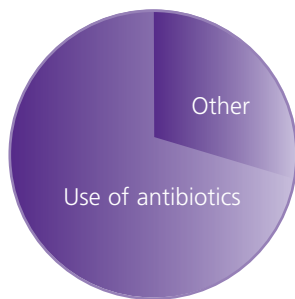
By Suzanne I. Singh, PharmD

Vulvovaginal candidiasis (VVC) is a common condition, and an estimated 75% of all women will experience an infection with candida yeast during their lifetime. Ninety percent of these infections are caused by *Candida albicans*.¹ The availability of nonprescription products for treatment of VVC allows pharmacists to play a role in counselling patients about when and how to self-treat and when to see a physician for evaluation or follow-up. Pharmacists must have an understanding of VVC, particularly its treatment options, so that they can make evidence-based recommendations to both patients and physicians.

FIRST-LINE AGENTS

On the basis of the evidence to date, azole antifungals may be considered as first-line agents for uncomplicated VVC, topical preparations being as effective as oral formulations, regardless of the duration of therapy.

Causes



Symptoms

- Mild to severe vaginal itching
- Abnormal vaginal discharge — minimal, “cheese-like” material, watery secretion
- Acute discomfort or vulvar, labial, or vaginal pain

Diagnosis

- Symptoms as above
- Observation of yeast on microscopy of vaginal fluid²

VVC is uncomplicated (approximately 90% of cases) or complicated (approximately 10%) (see Table 1).³

Symptoms can mask STD

An accurate diagnosis of VVC is essential to initiate appropriate treatment. A first episode with signs and symptoms suggestive of VVC should always be confirmed by a physician so that women are accurately diagnosed and, if needed, treated for a sexually transmitted disease such as herpes, human papilloma virus, gonorrhea, or chlamydia.

It may also be prudent to consider referral to a physician for women with recurrent infections. One study showed that only one third of women who self-diagnosed VVC actually met the diagnostic criteria for the condition, and that women with a previous diagnosis of VVC were no more accu-

rate in diagnosing subsequent infections than women without a previous diagnosis.⁴

Although VVC is not a sexually transmitted disease, women may benefit from their physician's guidance if cross-transmission of *C. albicans* from the sexual partner is a possibility.

Goals of treatment

The treatment of VVC with medication is aimed at resolving symptoms, eradicating infection, and preventing complications and recurrence.

A variety of antifungal agents have been used (see Table 2). Imidazole antifungals include clotrimazole, miconazole, and tioconazole, and tri-

azole antifungals including terconazole and fluconazole. Fluconazole is available orally, whereas the other azole antifungals are used intravaginally. Nystatin, a polyene antifungal agent, and boric acid have also been used intravaginally in the management of VVC.^{5,6}

The choice of antifungal for both uncomplicated and complicated forms of VVC should take into account the comparative efficacy, adverse effects, interactions, convenience, and cost of the available agents, as well as the woman's preference (so as to maximize adherence).

Uncomplicated VVC

Treatment with azoles results in relief of symptoms and negative results on culture in 80% to 90% of women with uncomplicated VVC who complete therapy.⁷ A review of 17 clinical trials found no statistically significant differences between oral and intravaginal azole antifungal treatments for clinical or mycological cure of uncomplicated VVC at short-term and long-term follow-up.⁸ Similarly, no statistically

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significant differences in clinical or mycological cure rates were observed between or within oral and intravaginal antifungal formulations administered as single-dose or multiple-dose treatments.⁸

Intravaginal nystatin may also be used for VVC, but it is generally considered a second-line agent since it is less active against *C. albicans* than the azole antifungals.² Intravaginal administration of boric acid capsules has also been effective, with cure rates of up to 90%, but this is generally considered a second-line agent because the capsules are not as readily available as the other drugs. Boric acid tends to be reserved for resistant VVC, for which it is very effective.⁶

Complicated VVC

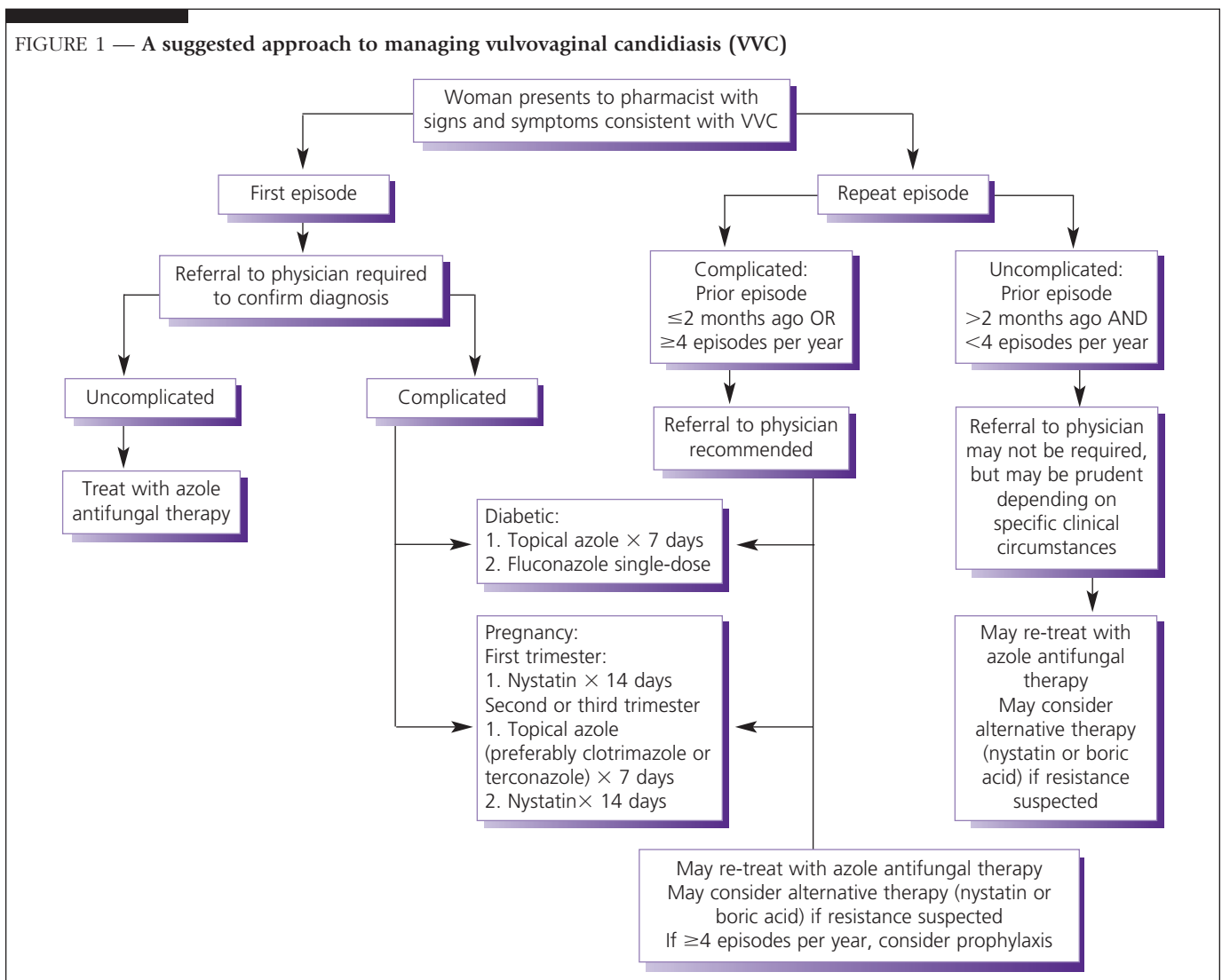
Diabetes mellitus: Diabetes mellitus may predispose women to VVC, and symptomatic infections may reflect uncontrolled diabetes.⁵ Increased glucose levels in the genital tissues enhance yeast adhesion and growth, and vaginal epithelial cells have a greater propensity to bind to *C. albicans* in women with diabetes than in those without this condition.⁹ There is a paucity of clinical trials

specifically examining the treatment of VVC in women with diabetes, so treatment recommendations have been extrapolated from evidence in women without diabetes.⁹ It is thought that women with uncontrolled diabetes may not respond as well to short-term therapies; efforts to improve glycemic control have been recommended, and a more prolonged duration of antifungal therapy (i.e., seven to 14 days) may be necessary.⁷

Pregnancy: Pregnant women may also be predisposed to VVC. It is thought that the increased susceptibility of the vagina to candida infection during pregnancy is related to elevated levels of glycogen and reproductive hormones. Candida strains have been cultured from the vagina in 10% to 20% of pregnant women, and the incidence of symptomatic VVC is two times higher in pregnant women than in women who are not pregnant.⁵ Gestational diabetes may also predispose a pregnant woman to VVC.

Topical agents have been recommended as first-line therapy for treatment of VVC in pregnancy.^{3,6,7,10} A systematic review found that triazole antifungals (e.g., terconazole) are as effective as imidazole antifungals (e.g.,

FIGURE 1 — A suggested approach to managing vulvovaginal candidiasis (VVC)



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TABLE 1 — Classification of vulvovaginal candidiasis (VVC)³

Feature	Uncomplicated VVC*	Complicated VVC†
Severity	Mild or moderate	Severe
Frequency	Sporadic	Recurrent
Organism	<i>Candida albicans</i>	Non-albicans species of <i>Candida</i>
Host	Normal	Abnormal (e.g., uncontrolled diabetes, pregnancy)

*A woman with all of these features is defined as having uncomplicated VVC
 †A woman with any of these features is defined as having complicated VVC

clotrimazole) when used during pregnancy.¹¹ Furthermore, data from five comparative studies suggested that imidazole antifungals are more effective than nystatin in the treatment of VVC in pregnancy.

Overall, single-dose azole treatment seemed as effec-

tive as three- and four-day azole treatment courses.¹¹ However, in two of the trials reviewed, which involved 81 women treated with azole antifungals, a seven-day treatment was more effective than a four-day treatment and as effective as a 14-day treatment. These data would suggest that a treatment course lasting approximately seven days may be preferred for pregnant women being treated with azole antifungals.¹¹

The safety of topical antifungals in pregnancy has been reviewed (see Table 3). Available data suggest that nystatin is the safest alternative during all trimesters of pregnancy because of minimal systemic absorption. Retrospective and prospective studies suggest that azole antifungals may be safe during pregnancy, although most manufacturers caution against their use during the first trimester because of limited experience.¹¹ Fluconazole is teratogenic and embryotoxic at high doses in rats and is assigned to risk category C by US Food and Drug Administration (category C means that either animal studies indicate a fetal risk and there have been no controlled studies of women, or there are no available

TABLE 2 — Antifungal agents used for vulvovaginal candidiasis^{3,5,6}

Drug	Formulation	Strength	Usual dosage*		
Nonprescription					
Clotrimazole (e.g., Canesten)	Vaginal cream	1%	One applicatorful vaginally HS × 6 nights		
		2%	One applicatorful vaginally HS × 3 nights		
		10%	One applicatorful vaginally HS × 1 night		
	Vaginal tablet	100 mg	One tablet vaginally HS × 6 nights		
		200 mg	One tablet vaginally HS × 3 nights		
		500 mg	One tablet vaginally HS × 1 night		
	Topical cream†	1%	Apply small amount to the vulva up to BID PRN × 7 days		
		Miconazole (e.g., Monistat)	Vaginal cream	2%	One applicatorful vaginally HS × 6 nights
			Vaginal suppository	100 mg	One suppository vaginally HS × 6 nights
	Vaginal ovule	400 mg	One ovule vaginally HS × 3 nights		
		1200 mg	One ovule vaginally HS × 1 night		
		Tioconazole (e.g., Gyneure)	Topical cream†	2%	Apply small amount to the vulva up to BID PRN × 7 days
Vaginal ointment	6.5%		One applicatorful vaginally HS × 1 night		
	Vaginal ovule	300 mg	One ovule vaginally HS × 1 night		
		Topical cream†	1%	Apply small amount to the vulva up to BID PRN × 7 days	
Boric acid (compounded by pharmacy)	Vaginal capsules	600 mg	One capsule vaginally once or twice daily × 14–28 days		
Prescription					
Nystatin (e.g., Mycostatin)	Vaginal cream	25,000 units/g	Apply 4 g vaginally HS × 14 nights		
Terconazole (e.g., Terazol)	Vaginal cream	0.4%	One applicatorful vaginally HS × 7 nights		
		0.8%	One applicatorful vaginally HS × 3 nights		
	Vaginal suppositories	80 mg	One suppository vaginally HS × 3 nights		
		Fluconazole (e.g., Diflucan)	Oral tablet	150 mg	One tablet orally × 1 dose

HS = at bedtime, BID = twice daily, PRN = as needed.
 *Medication should be continued throughout menstruation; consult product monographs for further information
 †Available in combination packs

TABLE 3 — Topical antifungal agents used intravaginally for VVC: considerations in pregnancy¹¹

Drug	FDA Pregnancy Risk Category	Systemic Absorption	Embryotoxic in Animals	Human Trials
Azole antifungals				
Clotrimazole (e.g., Canesten)	B	Up to 3% to 10%	Yes	Safe in second and third trimesters
Miconazole (e.g., Monistat)	C	1.4%	Yes	Possible increased risk of spontaneous abortion
Tioconazole (e.g., Gyne cure)	C	Negligible	Yes	No data
Terconazole (e.g., Terazol)	C	5% to 16%	Yes	Safe in second and third trimesters
Polyene antifungals				
Nystatin (e.g., Mycostatin)	A	Negligible	No data	Safe in all trimesters

FDA = US Food and Drug Administration.

reports of studies of women or animals). Observational evidence from humans and animals suggests a dose-related risk of teratogenicity in humans.¹¹ The benefits and risks of therapy with fluconazole must be weighed carefully because of the limited number of controlled studies in pregnant women.

Recurrent VVC

Fewer than 5% of women experience recurrent VVC (RVVC), defined as the occurrence of at least four specific episodes within one year or at least three episodes unrelated to antibiotic therapy within one year.¹² Species such as *Candida glabrata* and *Candida parapsilosis* are responsible for up to one-third of recurrent infections.¹

Each individual episode of RVVC caused by *C. albicans* responds well to short-duration oral or topical azole therapy. However, to maintain clinical and mycological control, specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or repeat dose of oral fluconazole three days after the first dose) to achieve mycological remission. Then, a maintenance antifungal regimen may be initiated. Suitable maintenance regimens include weekly administration of fluconazole or daily therapy with any topical azole.¹²

Antifungal resistance, which can lead to treatment failure, may be suspected in women experiencing RVVC. The options for managing resistance are limited. In general, agents with a different mechanism of action should be considered. Boric acid for the treatment of RVVC has been studied, and there is limited evidence for the use of nystatin.¹²

Adverse effects

The most common adverse effects associated with intravaginal azoles and nystatin are local irritation, stinging, burning, itching, and pain. These reactions may be related to the vehicle and not the actual drug itself.⁵

Irritation may be a dose-related effect and may be reduced by choosing a lower-strength formulation administered over a longer period.⁶

Irritation tends to be more common with intravaginal administration of boric acid than with other intravaginally administered drugs.⁶ Single-dose oral fluconazole is generally well tolerated, the most common adverse effect being stomach upset. Other, less common adverse reactions include dry mouth, rash, dizziness, and headache.⁵

Interactions

Topical formulations such as intravaginal creams and suppositories are oil-based and thus may weaken latex condoms and diaphragms.⁷ This increases the chances of a condom breaking during sexual intercourse, and the rubber in cervical caps or diaphragms may break down faster and wear out sooner. Women are generally advised to wait three days after treatment with an oil-based intravaginal product before using a condom or diaphragm;¹³ they should refer to condom product labelling for further information.

Although uncommon, a clinically significant interaction between topical miconazole and warfarin may occur. Although there is minimal systemic absorption of miconazole in healthy women of child-bearing age, it is hypothesized that vaginal atrophy may be partly responsible for altered systemic uptake of this drug.^{14,15} Miconazole may inhibit cytochrome P450 3A4 and 2C9 isoenzymes and thus inhibit the metabolism of warfarin. This interaction may result in elevated international normalized ratios (INRs) and increase the risk of bleeding in women taking warfarin. If this drug combination is used, consideration should be given to increasing the frequency of INR monitoring (e.g., every two days), and the woman should monitor for symptoms of bleeding.⁶

Fluconazole is another drug that inhibits cytochrome P450 3A4 and 2C9 isoenzymes, and clinically significant

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interactions between fluconazole and drugs metabolized via this route (e.g., warfarin) may therefore occur.⁵ Clinically significant hypoglycemia may be precipitated by the use of fluconazole in combination with oral hypoglycemic agents; one death has been reported because of hypoglycemia occurring in association with combined use of fluconazole and glyburide. In pharmacokinetic studies, clinically significant hypoglycemia was observed when fluconazole was used for a period of seven days.

Blood glucose concentrations should be monitored if fluconazole is used concomitantly with oral sulfonylureas for a prolonged duration.¹⁶

Summary

Optimal treatment for VVC depends on whether the infection is uncomplicated or complicated. (A suggested approach to managing VVC is illustrated in Figure 1.) ■

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